PCT

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [6] : C07C 401/00	A1	(11) International Publication Number: **WO 96/01811** (43) International Publication Date: 25 January 1996 (25.01.96)

(21) International Application Number: PCT/US95/07595 (22) International Filing Date: 22 June 1995 (22.06.95) (30) Priority Data: 08/272,665 11 July 1994 (11.07.94) US (71) Applicant: THE JOHNS-HOPKINS UNIVERSITY [US/US]; 3400 N. Charles Street, Baltimore, MD 21218 (US). (72) Inventor: POSNER, Gary, H.; 3216 Timberfield Lane, Baltimore, MD 21208 (US). (74) Agents: KOKULIS, Paul, N. et al.; Cushman Darby & Cushman L.L.P., 1100 New York Avenue, N.W., Washington, DC 20005 (US).	(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). **Published** *With international search report.*

---

(54) Title: 2-SUBSTITUTED 1,25-DIHYDROXYVITAMIN D3 DERIVATIVES

(57) Abstract

Vitamin D3 analogues which include a 2-substituted alcohol or fluoride are described. The preferred alcohol substituent is exemplified by the structural formula $-(CH_2)_4OH$ and the preferred fluoride substituents by the structural formulas $-(CH_2)_3F$ and $-(CH_2)_4F$. Methods for the preparation of a vitamin D3 analogue which includes a 2-substituted alcohol or fluoride starting with 2+4-cycloaddition of commercially available methyl 2-pyrone-3-carboxylate are also described.

2-SUBSTITUTED 1,25-DIHYDROXYVITAMIN D₃ DERIVATIVES

BACKGROUND OF THE INVENTION

The present invention relates to novel
biologically active vitamin D_3 analogues which
include an alcohol or fluoride substituent in the
2-position and methods for their preparation.

FIELD OF THE INVENTION

Vitamin D_3 analogues have been recognized as
having important biological activities. It is
known, for example, that vitamin D_3 analogues can
be used to control calcium and phosphate
metabolism.

It is also known that such analogues are
useful for inducing cell differentiation and for
inhibiting undesired cell proliferation. For
example, it is well recognized that vitamin D_3
produces 1α,25-dihydroxyvitamin D_3 (calcitriol)
during normal metabolism. Calcitriol is a potent
regulator of cell differentiation and
proliferation as well as intestinal calcium and
phosphorus absorption and bone calcium
mobilization. Calcitriol is also known to affect

the immune system and this compound, as well as a
·variety of synthetic vitamin D_3 derivatives have
been used in practical, clinical chemotherapy of
such diverse human illnesses as osteoporosis,

5.   cancer, immunodeficiency syndromes and skin
disorders such as dermatitis and psoriasis.
However, major research efforts are underway in an
effort to prepare vitamin D_3 analogues as drugs in
which calcitropic activity is effectively

10   separated from cell growth regulation.

     Calcitriol may be structurally represented as
follows:
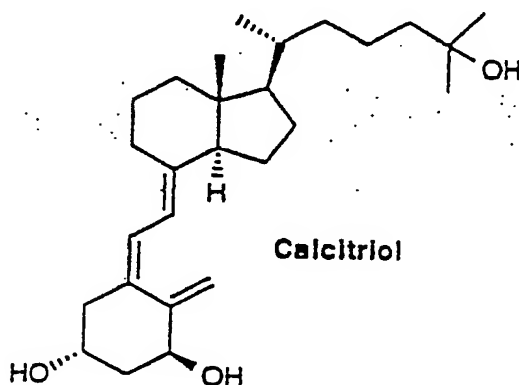
Calcitriol

     The upper and lower ring portions of
calcitriol may be called, for ease of reference,

15   the C/D-ring and A-ring, respectively.

DESCRIPTION OF THE RELATED ART

Especially for post-menopausal women, osteoporosis is a very serious illness that causes physical deformity and high susceptibility to bone (e.g., hip) fractures. In the general population aged above 65 years, osteoporosis ranks third to heart disease and cancer in terms of prevalence[1]. It is estimated that 30% of women at 75 years and 40% of women at 85 years have abnormal bone loss[2]. Calcitriol is being used, especially in Japan where dietary intake of calcium is low, for treatment of osteoporosis[3]. The Chugai Pharmaceutical Company has developed ED-71 (1) as a synthetic derivative of calcitriol, having a batter therapeutic index than calcitriol[4]. This 2ß-(3'-hydroxypropyloxy)-calcitriol has a two-fold stronger binding affinity to the rat plasma vitamin D-binding protein (DBP) than does calcitriol, suggesting that it circulates in the plasma with a longer half-life than calcitriol[4]. Furthermore, in animal models with osteoporosis, ED-71(1) is more effective than calcitriol[4].

To probe structure-medicinal activity relationships in the hope of preparing a new osteoporosis drug with an even better therapeutic index than ED-71(1), we targeted the 2-carba-analogues 2 and 3, structurally represented below.

These analogues were chosen because replacing one
oxygen atom by a methylene group, a relatively
small change in a large steroid molecule, was
anticipated, based on the current working model

5   for receptor binding of ED-71(1)[4], not to interfere
with such critical receptor binding. also, these
analogues were chosen for chemical reasons,
probing whether recently developed Diels-Alder
methodology[5] using 2-pyrones and monosubstituted

10 alkenes could be extended to 1,2-disubstituted
alkene dienophiles with reliable and faithful
transfer of olefin geometry ultimately into the
stereochemical relationships at the 1- and 2-
positions of the steroid targets. We record here

15 the results of these chemical explorations and
biological evaluations.

Calcitriol

1, X = β - O (ED-71)
2, X = β - CH$_2$
3, X = α - CH$_2$

- 4 -
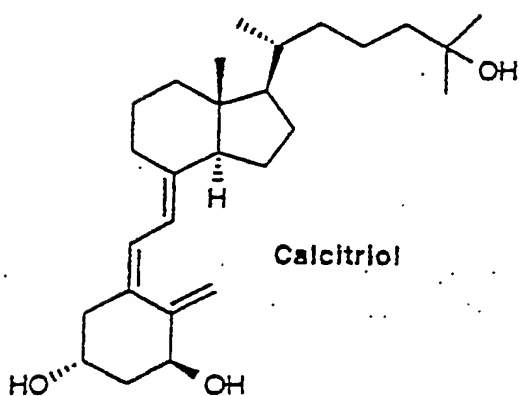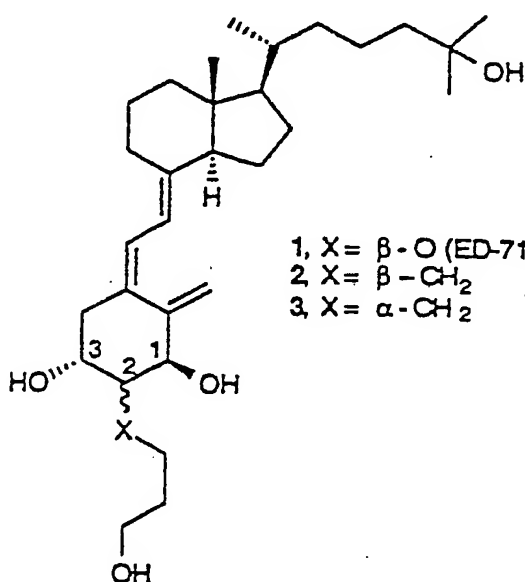
SUMMARY OF THE INVENTION

The present invention is for a vitamin D_3 analogue which includes a 2-substituted alcohol or fluoride. The preferred alcohol substituent is exemplified by the structural formula $-(CH_2)_4OH$ and the preferred fluoride substituents by the structural formulas $-(CH_2)_3F$ and $-(CH_2)_4F$.

The preferred diastereomers of the 2-substituted $-(CH_2)_4OH$ are represented by the following structural formulas:
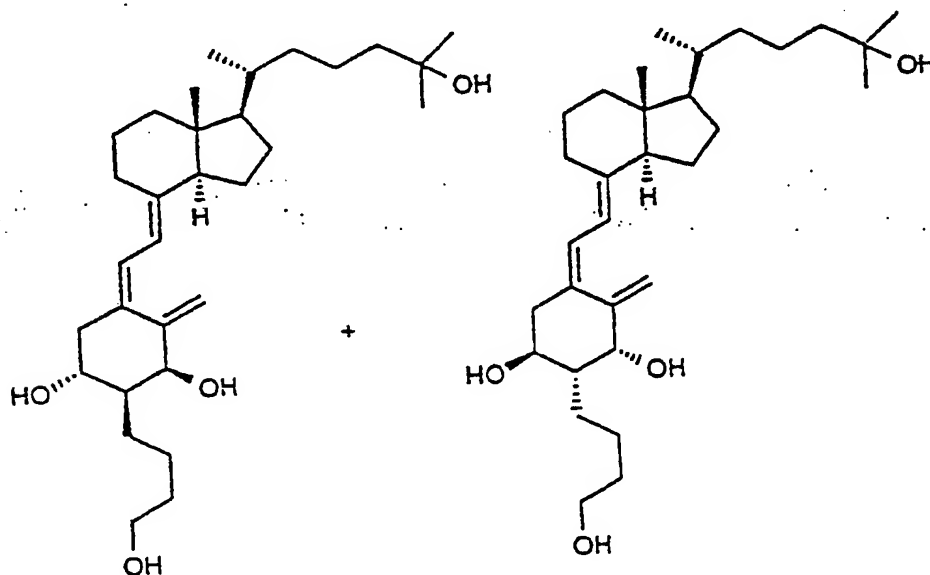
The present invention is also for the related method of preparation of a vitamin D_3 analogue which includes a 2-substituted alcohol or fluoride starting with 2+4-cycloaddition of commercially available methyl 2-pyrone-3-carboxylate.

- 5 -

Diastereomeric 2-substituted calcitriol
analogues were prepared in only eleven chemical
operations, starting with 2+4-cycloaddition of
commercially available methyl

5   2-pyrone-3-carboxylate. Highlights of this
convergent and stereo controlled synthetic
approach are as follows: (1) retention of reactant
dienophile geometry in the product bicyclic
lactone, characteristic of a concerted

10   inverse-electron-demand Diels-Alder cycloaddition;
(2) an improved decarboxylation procedure
involving chemospecific allyloxide opening of a
lactone ring in the presence of a methyl ester and
then non-high pressure palladium-promoted allylic

15   ester decarboxylation; and (3) use of the
enantiomerically pure C,D-ring chiron 14 to
resolve racemic A-ring phosphine oxide 13.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED
EXEMPLARY EMBODIMENTS

20   Uncatalyzed Diels-Alder cycloadditions
between highly polarized dienes and dienophiles
can occur step-wise rather than in the usual
concerted fashion[6]. To probe this issue within the
context of inverse-electron-demand Diels-Alder

25   cycloadditions using 2-pyrones substituted at the
3-position with highly electron-withdrawing (e.g.

- 6 -

3-sulfonyl, 3-acyl) substituents[5], 3-p-
toluenesulfonyl-2-pyrone and 1,2-disubstituted
alkenes 4E and separately 4Z were placed under
high pressure.   In both of these electronically

5   matched cases, the electron-poor 2-pyrone diene
and the electron-rich vinylic ether cycloadded to
produce isolable bicyclic lactone adducts without
undesirable and often-encountered extrusion of CO_2
(Scheme I)

10   The most important aspect of these Diels-
Alder reactions from a mechanistic viewpoint is
that the cycloadducts retained the stereochemical
information in the reactant vinylic ethers:
dienophile 4E led exclusively to trans-4,5-

15   oriented products 5a and 5b, whereas dienophile 4Z
led exclusively to cis-4,5-oriented products 6a
and 6b.   Therefore, these polarized 2+4-
cycloadditions must occur in a concerted rather
than in a step-wise fashion[6].   The assignments of

20   the 4,5-positional relationships were based on
extensive precedent[5], and the assignments of the
4,5-stereochemical relationships were based on the
match of the 400 MHz ^{1}H NMR $J_{4,5}$ coupling constants
with those calculated using the Karplus equation

25   for energy-minimized structures generated using
Chem-3D (Scheme I)[7].   Bicyclic lactone 6a, the very
major cycloadduct, differed in a characteristic
way[5] from bicyclic lactone 6b in terms of the

SCHEME I
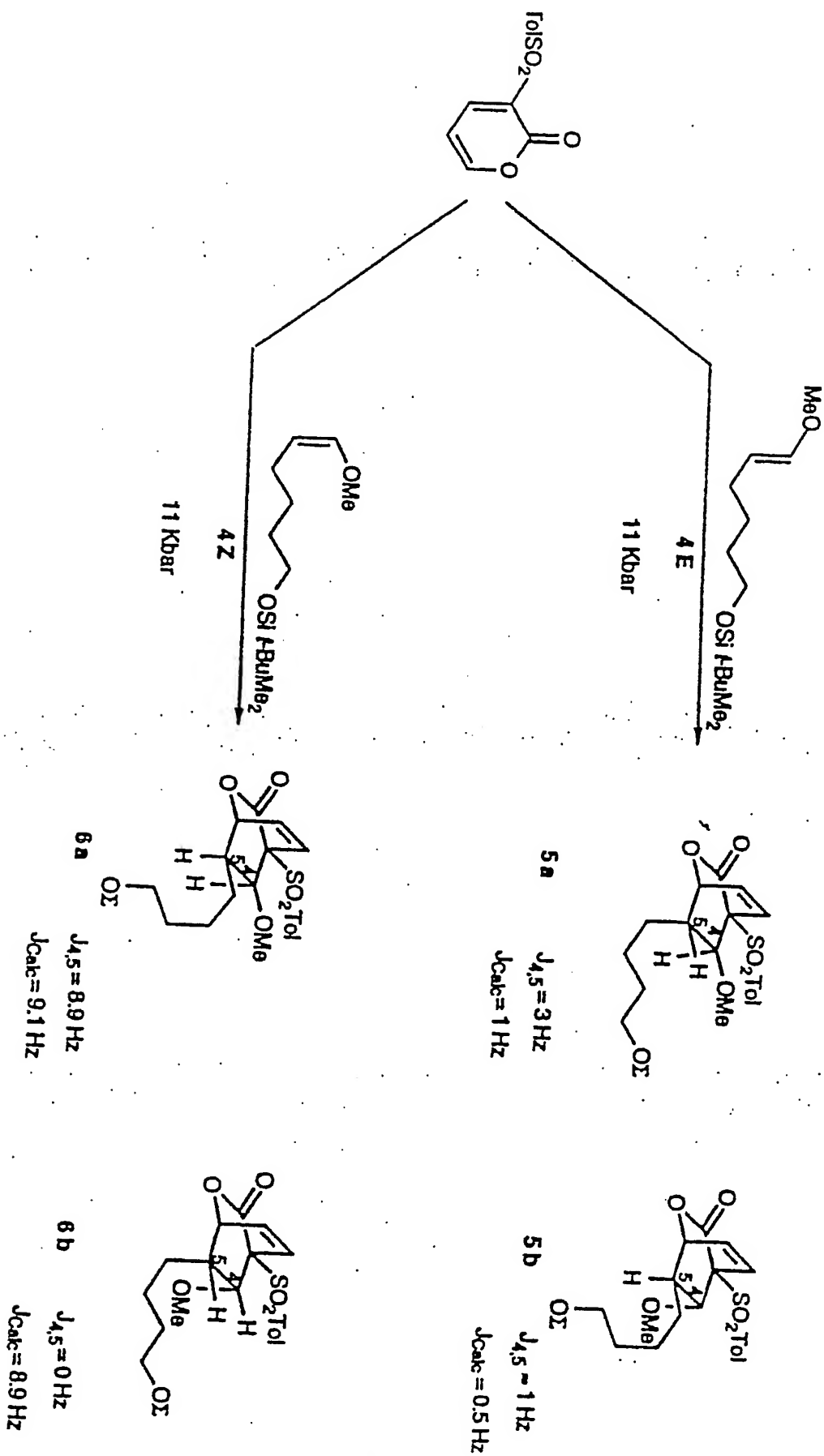
chemical shift of the bridgehead hydrogen atom (δ 4.98 vs. 5.04) and the chemical shift of the C_4 hydrogen atom (δ 4.55 vs. 3.83). Also, irradiation of the C_5 hydrogen atom of lactone 6a caused an 11 % nOe on the C_4 hydrogen atom. The large discrepancy between the observed and the calculated $J_{4.5}$ coupling constant for cis-4.5-disubstituted bicyclic adduct 6b was of considerable concern. Therefore, a series of similar cis-4.5-disubstituted bicyclic lactones was prepared. Examination of their $J_{4.5}$ coupling constants (Table I) showed a very subtle effect of the nature of the substituents on this magnitude of the vicinal coupling constant. For example, the cycloadduct derived from the 6-membered cyclic vinyl ether showed $J_{4.5}=0$ Hz (entry 2), whereas that derived from the 5-membered cyclic vinyl ether showed $J_{4.5}=8.5$ Hz (entry 3). Finally, based on literature analogies in which E-alkenes underwent 2+4-cycloadditions more easily than Z-alkenes[6e-g], we were surprised to find that vinylic ether geometric isomer 4Z reacted considerably faster than isomer 4E with 3-tolysufonyl-2-pyrone. Whereas vinylic ether isomer 4Z yielded almost exclusively the endo-cycloadduct 6a, as expected from previous results[5], vinylic ether isomer 4E gave a 1:2 mixture of cycloadducts 5a:5b.

TABLE I

¹H NMR Data for Several *cis*-4,5-Disubstituted Bicycloadducts
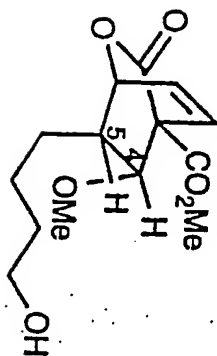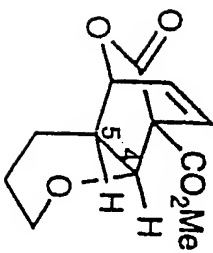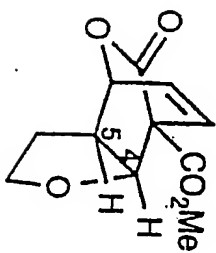
Entry	Compound	$J_{4,5}$ (Hz)
1		0
2		0
3		8.5

From a synthesis viewpoint, cycloadducts **5**
and **6** turned out to be disappointing. Despite
close structural similarity with other bridgehead-
substituted toluenesulfonyl cycloadducts and
related cyclohexene systems that underwent smooth
reductive-desulfonylation[8], we were unsuccessful
using a variety of conditions (e.g., Al-Hg, Na-Hg,
Raney nickel, Li/NH$_3$) to effect high-yielding
reductive-desulfonylation. Also, it was
anticipated that ultimate conversion of the methyl
ether functionality into the desired alcohol group
would be more difficult than deprotection of a
silyl ether. Therefore, silylated vinylic ether
7Z, prepared according to literature precedent as
illustrated in Scheme II[9], and commercially
available methyl 2-pyrone-3-carboxylate were
subjected to high pressure cycloaddition (eq. 1).

Bicycloadduct **8** was the major product,
isolated on gram scale in 60% yield, with the
oxygen substituted at position-4, as expected
based on the polar nature of the Diels-Alder
cycloaddition and also on literature precedent[5],
with a cis-4,5-stereochemical relationship. This
stereochemical outcome was expected based on the
results in Scheme I with the 3-sulfonyl-2-pyrone
and was confirmed by the observed large ^{1}H NMR $J_{4,5}$
coupling constant (8.6 Hz)[7] and by the
characteristic chemical shifts of the bridgehead

SCHEME II
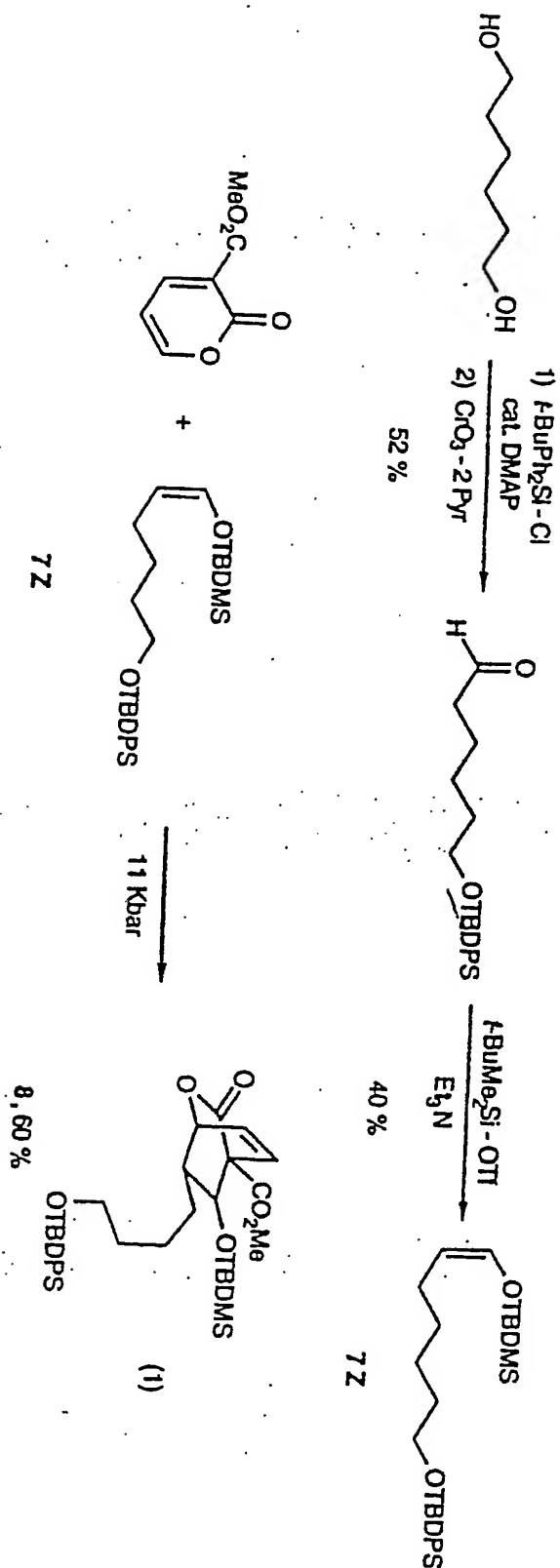
hydrogen atom at δ 5.1 and the C_4 hydrogen atom at δ 4.7. Also, irradiation of the C_5 hydrogen atom caused a 14% nOe on the C_4 hydrogen atom, confirming their cis-4,5-relationship. We have not succeeded in preparing cleanly the isomeric silylated vinylic ether 7E for cycloaddition with methyl 2-pyrone-3-carboxylate.

Having served its chemical function of activating the pyrone diene (the unsubstituted parent 2-pyrone is unreactive)[5d,10] for cycloaddition with the electron-rich vinylic ether 7Z, the bridgehead carboxylate ester group in bicyclic lactone adduct 8 had to be removed. To complement our two-step lactone methanolysis and high-pressure procedure for this type of decarboxylation[11], we report now a new and more convenience (i.e., not high pressure) two-step protocol (Scheme III). Although bicyclic lactone methyl ester 8 has two ester carbonyl groups, it was gratifying to find that the lactone ring was chemospecifically attacked by lithium allyloxide to produce mixed methyl allyl malonate 9 in 75% yield. In accord with literature precedent[12], allyl ester 9 was smoothly decarboxylated using palladium acetate; an unexpected but desired benefit of this procedure was conjugation of the cyclohexene double bond, giving the contiguously

SCHEME III

8

1)
2) tBuMe₂Si - OTf

65 %

9

Pd(OAc)₂, PPh₃
HCO₂H Et₃N

92 %

10

- 14 -
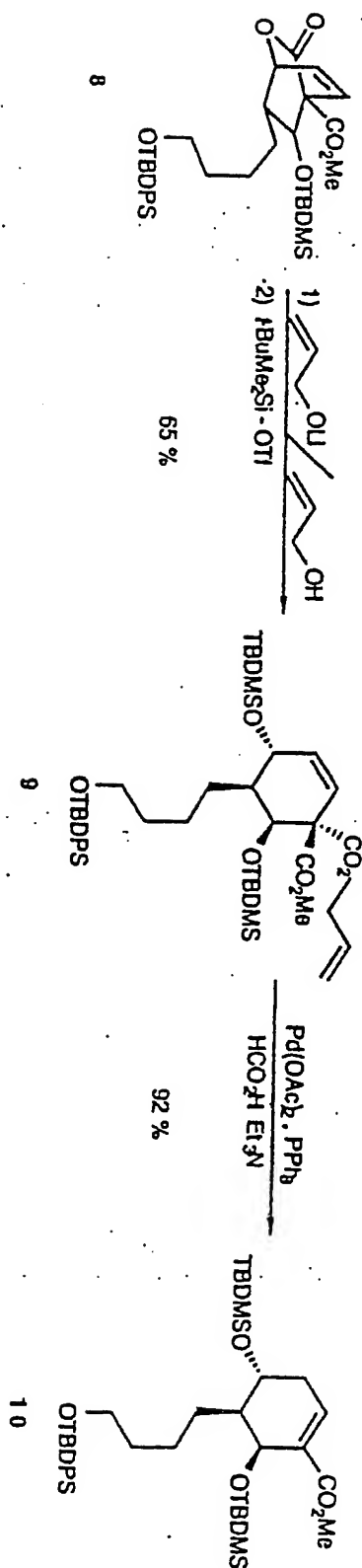
tetrasubstituted cyclohexene 10 in 92% yield
(Scheme III).

Without any surprises, highly functionalized
cyclohexene alcohol ester 10 was O-silylated and

5   then reduced to form allylic alcohol 11 (Scheme
IV). One flask Claisen rearrangement followed by
spontaneous thermal sulfoxide elimination was
achieved using our sulfinylated ortho ester
protocol[13] giving an unusually favorable >10:1 Z:E

10   ratio of dienoate esters from which the desired Z-
dienoate 12 was isolated by chromatography in 80%
yield.

Established reactions as outlined in Scheme
IV below provided the crucial, fully O-protected,

15   racemic, A-ring phosphine oxide 13. Lythgoe-type
coupling[14] of the conjugate base of phosphine oxide
13, generated using phenyllithium[15], with C,D-ring
ketone 14 of natural absolute configuration
produced O-silylated derivatives of diastereomeric

20   2-(4'-hydroxylated) calcitriol analogues 3 and 3',
isolated in 50% yield.

Fluoride-induced cleavage of the silyl
protecting groups proceeded easily at three of the
four silylated alcohol groups; desilylation at the

25   C_1 secondary alcohol position, however, was
unexpectedly slow, requiring considerably more
vigorous reaction conditions.

In another context[16], we have observed that the C_1 secondary alcohol unit in calcitriol is chemically less reactive than the C_3 secondary alcohol toward esterifying reagents.

5   Nevertheless, fluoride-assisted quadruple desilylation under more vigorous conditions eventually yielded the desired calcitriol analogues 3 and 3'.

Easy HPLC separation gave each diastereomer
10 in enantiomerically pure form.   Tentative assignments of stereochemistry to diastereomers 3 and 3' were made by ^{1}H NMR in analogy with closely related calcitriol analogues; in diastereomeric pairs differing only by inversions of
15 stereochemistry at positions 1-3 but not in the C,D-ring or in the side chain, the 1α-substituted diastereomer characteristically showed a lower field absorption for the C_{18}-methyl group and for one proton of the C_{19}-methylene group (Table II).

TABLE II.

^{1}H NMR Chemical Shift (δ)

	1	2	3	C$_{18}$	C$_{19}$	Ref
	α-OH	β-OH	β-OH	0.54	5.14	17
	β-OH	α-OH	α-OH	0.53	5.11	17
	α-CH$_2$OH	–	β-OH	0.54	5.02	15
	β-CH$_2$OH	–	α-OH	0.50	4.99	15
	α-CH$_2$CH$_2$OH	–	β-OH	0.54	4.90	13b
	β-CH$_2$CH$_2$OH	–	α-OH	0.51	4.88	13b
3	1α-OH	2α-(CH$_2$)$_4$OH	β-OH	0.54	5.00	this
3'	1β-OH	2β-(CH$_2$)$_4$OH	α-OH	0.52	4.98	work

Thus, in only 11 steps from commercially
available methyl 2-pyrone-3-carboxylate, two new
vitamin D_3 analogues have been prepared, and the
C,D-ring chiron **14** has been used to resolve
5   racemic A-ring phosphine oxide **13**.

SCHEME IV
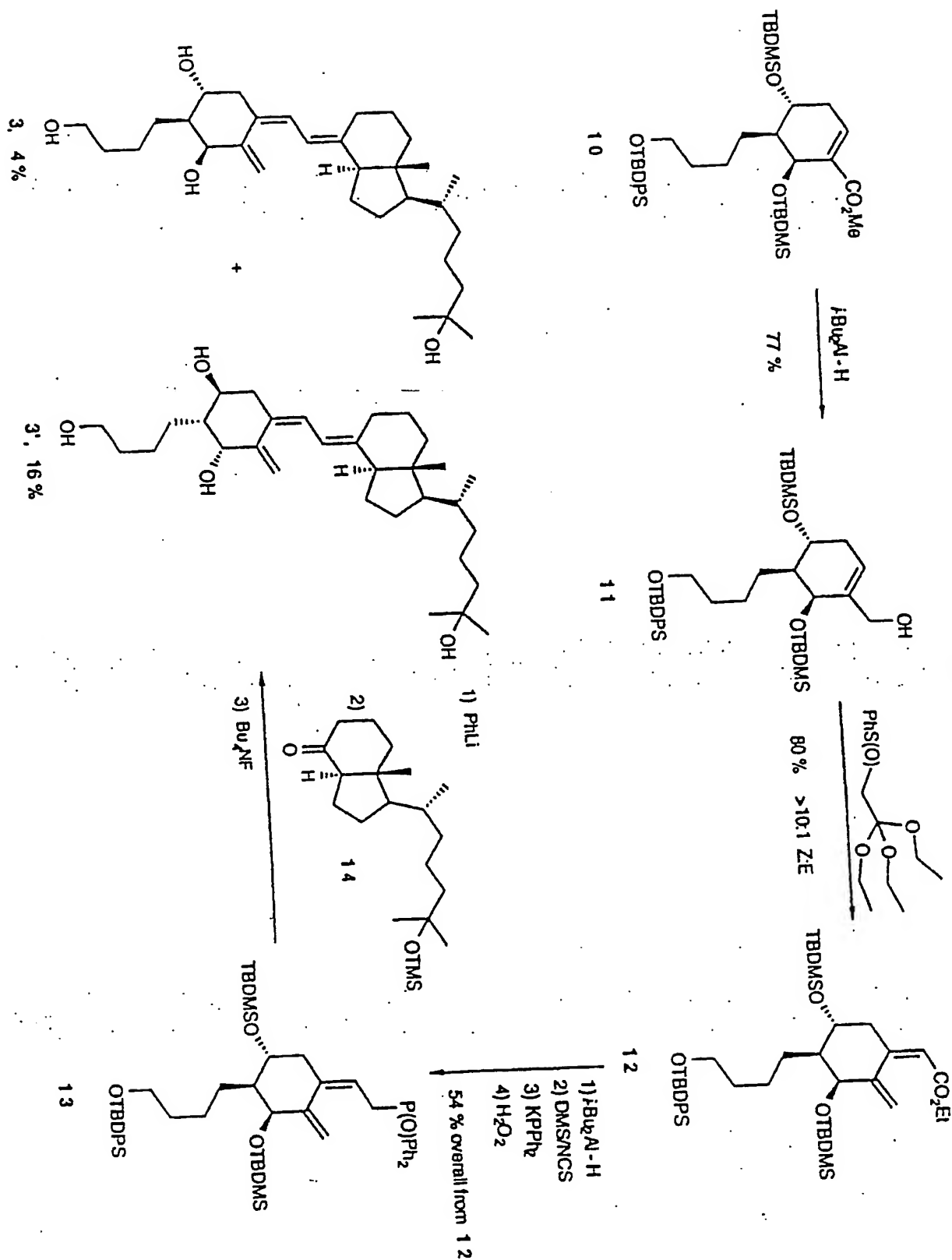
Preliminary biological evaluation of synthetic diastereomers 3 and 3' involved measuring their relative binding affinities to rat vitamin D binding protein (DBP) and also to the

5   vitamin D receptor of bovine thymus (Table III). Diastereomer 3 had significantly higher affinity than ED-71 (1) for the vitamin D binding protein, but it had extremely low affinity for the vitamin D receptor; whether this separation of binding

10   affinities has important mechanistic and/or medicinal value remains to be established. Diastereomer 3', on the other hand, had lower affinity than ED-71 (1) for the vitamin D binding protein, but it had higher affinity than ED-71 (1)

15   for the vitamin D receptor. Determining the impact of these differences on possible use of these new analogues for chemotherapy of osteoporosis requires further biological testing.

TABLE III.

20   RELATIVE BINDING AFFINITIES

	DBP	D RECEPTOR
$25(OH)-D_3$	90	---
$1,25(OH)_2-D_3$	1	1
Ed-71(1)	3.7	0.21
3	5.0	0.01
3'	1.9	0.28

Relative binding affinities of diastereomers

3 and 3' to the vitamin D binding protein and to

the vitamin D receptor showed some unusual trends.

Diastereomer 3' surprisingly bound much more

5   effectively to the vitamin D receptor than did the

established osteoporosis drug candidate ED-71 (1).

EXAMPLES

General

Tetrahydrofuran and diethyl ether were

10   distilled from benzophenone ketyl prior to use.

Methylene chloride and triethylamine were

distilled from calcium hydride immediately prior

to use. Commercially available anhydrous solvents

were used in other instances. All reagents were

15   purchased from Aldrich Chemical Co. (Milwaukee,

WI) and unless otherwise specified were used as

received without further purification. All

reactions were run in flame-dried flasks under

nitrogen unless otherwise specified. FT-IR

20   spectra were determined using a Perkin-Elmer Model

1600 FT-IR spectrophotometer. The ^{1}H NMR were

recorded on a Varian XL-400 spectrometer and

Bruker AMX-300 spectrometer operating at 400 and

300 MHz, respectively. The ^{13}C spectra were

25   recorded on the same instruments operating at 100

and 75 MHz, respectively. High resolution mass

spectra were obtained on a two sector-high-

resolution VG-70S mass spectrometer run at 70 eV.
A Leco Corp. Model No. PG-200-HPC 13 Kbar
apparatus was used for the high-pressure studies.

Silylated Vinylic Ether 7Z

5   To a 100 mL round-bottomed flask containing
2.1 g (17.5 mmol) of 1,6-hexanediol, 2.7mL (19.2
mmol) of triethylamine, and 10 mg of N,N-
dimethylaminopyridine in 35 mL CH_2Cl_2 was added 5
mL (19.2 mmol) of t-butylchlorodiphenylsilane.

10   The reaction was stirred at room temperature for
12 h, or until complete by TLC. The reaction was
quenched with 10 mL water, the organic layer was
separated, and the aqueous layer was washed with
CH_2Cl_2. The combined organic layers were dried

15   over $MgSO_4$, filtered, and concentrated. The crude
product was purified by column chromatography (10-
20% EtOAc/Hexane) to afford 3.73 g (10.45 mmol,
60% yield) of the monosilated product as a clear
oil.

20   To a 250 mL round-bottomed flask containing
10.14 mL (125.4 mmol) of pyridine in 50 mL of
CH_2Cl_2 was slowly added 6.27 g (62.7 mmol) of
chromium trioxide. The resultant deep burgundy
solution was stirred for 15 minutes at room

25   temperature. At the end of this period, a
solution of the above monosilated diol in 50 mL
CH_2Cl_2 was added via cannula. A tarry, black

deposit separated immediately. This mixture was
stirred for 1h at which time the CH_2Cl_2 was removed
on a rotary evaporator and the tar was diluted
with Et_2O. This heterogeneous mixture was filtered

5   through silica gel to give a yellow liquid which
was concentrated. The crude product was purified
by column chromatography (5% EtOAc/Hexane) to give
3.17 g (8.9 mmol, 85% yield) of the aldehyde as a
clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H),

10   7.675 (m, 4H), 7.40 (m, 6H), 3.66 (t, J=6.2 Hz,
2H), 2.34 (m, 2H), 1.58 (m, 4H), 1.41 (m, 2H),
1.04 (s, 9H), IR ($CHCl_3$) 3013 cm^{-1}, 2931 cm^{-1}, 1713
cm^{-1}.

The above aldehyde was then diluted with 20

15   mL of benzene and 1.64 mL (11.75 mmol) of
triethylamine. The resulting mixture was cooled
to 0°C and 2.45 ml (10.68 mmol) of t-
butyldimethylsilyl triflate was added. The
reaction was allowed to warm to room temperature

20   and stirred for 1 h. The reaction was quenched
with brine and diluted with Et_2O. The organic
layer was separated, and the aqueous layer was
washed with Et_2O. The combined organic layers were
dried over $MgSO_4$, filtered, and concentrated. The

25   crude product was purified by column
chromatography (Hexane) or silica gel that was
slurry-packed with 1% triethylamine/hexane. The
silylated vinylic ether 7Z (1.67 g, 3.56 mmol, 40%

yield) was a clear oil; R_f=0.8 (25% EtOAc/Hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65 (m, 4H), 7.41 (m, 6H), 6.17 (dt, J=5.9, 1.5 Hz, 1H), 4.43 (dd, J=7.4, 5.9 Hz, 1H), 3.61 (t, J=6.6 Hz, 2H), 2.09 (ddt, J=14.7, 7.4, 1.5 Hz, 2H), 1.54 (m, 2H), 1.37 (m, 2H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 138.50, 135.54 (4), 134.15 (2), 129.50, 129.43, 127.55 (2), 127.53, 110.54, 63.93, 32.31, 26.87 (3), 25.99 (3), 25.80, 25.66, 23.36, 19.22, -2.92, -5.36; IR (CHCl$_3$) 3013, 2931, 1654, 1108 cm^{-1}; HRMS m/e calcd. for $C_{24}H_{35}O_2Si_2$ 411.2176, found 411.2179.

Cycloadduct 8

A 12 cm piece of 3/8" heat shrinkable teflon tubing (Ace Glass cat. #12685-40) was sealed on one end with a glass dowel plug by using a heat gun. To this 500.0 mg (3.24 mmol) of methyl 2-pyrone-3-carboxylate (Aldrich), 2g (4.26 mmol) of silylated vinylic ether 7Z, 10 mg of barium carbonate, and 2 mL of dry CH$_2$Cl$_2$ was added. The open end of tubing was then sealed in a similar fashion with a second glass dowel plug. This 'sealed tube' was the pressurized at 10-11 Kbar at room temperature for 4 days. The reaction mixture was concentrated on a rotary evaporator and the residue was purified by column chromatography (5% EtOAc/Hexane) to give 1.21 g (1.94 mmol, 60%) of

the cycloadduct 8 as a clear oil; R_f=0.58 (25%

EtOAc/Hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65 (m,

4H), 7.41 (m, 6H), 6.78 (dd, J=7.8, 2.8 Hz, 1H),

6.46 (dd, J=7.8, 5.1 Hz, 1H), 5.09 (ddd, J=5.1,

5   3.8, 1.0 Hz, 1H), 4.71 (dd, J=7.6, 1.00 Hz, 1H),

3.89 (s, 1H), 3.66 (t, J=6.1 Hz, 3H), 2.35 (ddd,

J=7.6, 3.8, 2.8 Hz, 1H), 1.56 (m, 2H), 1.26 (m,

2H), 1.06 (s, 9H), 0.91 (m, 2H), 0.78 (s, 9H),

0.012 (s, 3H), 0.006 (s, 3H); ^{13}C NMR (75 MHz,

10   CDCl$_3$) δ 168.93, 167.51, 135.51 (4), 133.70 (2),

130.46, 129.53 (2), 128.64, 127.54 (4), 76.12,

69.36, 63.12, 52.7, 44.72, 32.37, 27.09, 26.75

(3), 25.64 (3), 25.56, 25.31, 23.34, 19.09, 18.04,

-3.90, -5.03, IR (CHCl$_3$) 1760, 1743 cm^{-1}; HRMS m/e

15   calcd. for C$_{31}$H$_{41}$O$_6$Si$_2$ 565.2442, found 565.2450.

Mixed Malonate 9

To a 25 mL round-bottomed flask with 500 mg

(0.80 mmol) of cycloadduct 8 and 2 mL of CH$_2$Cl$_2$ at

0°C was added dropwise, via syringe, 962 μL of a

20   freshly made 1.0 M solution of lithium allyloxide

in allyl alcohol. The reaction mixture was

allowed to warm to room temperature after the

addition. Reaction was complete by TLC after 2

hours. The mixture was quenched with 2 mL aq.

25   NH$_4$Cl and extracted with CH$_2$Cl$_2$. The organic layer

was dried with MgSO$_4$, filtered, and concentrated on

a rotary evaporator. The residue was purified by

column chromatography (0-20% EtOAc/Hexane) to give

410 mg (0.60 mmol, 75%) of the desired malonate as

a clear oil; R_f=0.42 (25% EtOAc/Hexane); ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.96

(s, 2H), 5.83 (ddt, J=17.2, 10.5, 5.6 Hz, 1H),

5.36 (dd, J=17.2, 1.5 Hz, 1H), 5.22 (dd, J=10.5,

1.5 Hz, 1H), 4.76 (s, 1H), 4.63 (ddt, J=13.3, 5.6,

1.4 Hz, 1H), 4.51 (ddt, J=13.3, 5.6, 1.4 Hz, 1H),

4.02 (t, J=8.6 Hz, 1H), 3.74 (s, 3H), 3.69 (t,

J=6.1 Hz, 2H), 1.71 (m, 2H), 1.64 (m, 2H), 1.57

(s, 1H), 1.28 (m, 2H), 1.05 (s, 9H), 0.81 (s, 9H),

0.07 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 169.11, 167.95, 135.41 (4), 134.07 (2),

133.89, 131.17, 129.34 (2), 127.44 (4), 122.47,

118.43, 71.70, 68.64, 65.72, 63.89, 61.38, 52.57,

46.04, 32.45, 26.76 (3), 25.94 (3), 23.25, 19.04,

18.27, 14.02, -3.79, -4.44; IR ($CHCl_3$) 1737 cm^{-1};

HRMS m/e calcd. for $C_{34}H_{47}O_7Si_2$ 623.2860, found

623.2865.

To a 25 mL round-bottomed flask with 380 mg

(0.56 mmol) of the allyl ester alcohol, 78 μL

(0.67 mmol) of 2,6-lutidine, and 1.5 mL of CH_2Cl_2

at 0°C was added 154 μL (0.67 mmol) of t-

butyldimethylsilyl trifluoroethanesulfonate

dropwise via syringe. The reaction was complete

by TLC after 10 minutes. The reaction was

quenched at 0°C with 1 mL water and allowed to

warm to room temperature. Extraction with CH_2Cl_2

followed by drying with $MgSO_4$, filtration, and
concentration afforded a viscous oil which was
purified by column chromatography (5%
EtOAc/Hexane) giving 390 mg (0.49 mmol, 87%) of O-
silylated mixed malonate 9 as a clear oil; R_f=0.6
(25% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68
(m, 4H), 7.41 (m, 6H), 5.87 (d, J=2.68 Hz, 2H),
5.83 (ddt, J=17.2, 10.5, 5.6 Hz, 1H), 5.36 (dd,
J=17.2, 1.5 Hz, 1H), 5.22 (dd, J=10.5, 1.5 Hz,
1H), 4.76 (s, 1H), 4.63 (ddt, J=13.3, 5.6, 1.4 Hz,
1H), 4.51 (ddt, J=13.3, 5.6, 1.4 Hz, 1H), 4.13 (d,
J=9.2 Hz, 1H), 3.74 (s, 3H), 3.69 (t, J=6.1 Hz,
2H), 1.76 (m, 2H), 1.61 (m, 2H), 1.55 (s, 1H),
1.28 (m, 2H), 1.06 (s, 9H), 0.88 (s, 9H), 0.83 (s,
9H), 0.08 (s, 3H); 0.06 (s, 3H), 0.04 (s, 3H), -
0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.27,
167.96, 135.45 (4), 133.99 (2), 133.97, 131.33,
129.38 (2), 127.48 (4), 121.83, 118,43, 71.70,
69.16, 65.69, 64.00, 61.47, 52.52, 46.10, 32.67,
26.81 (3), 25.99 (3), 25.80 (3), 23.25, 19.10,
18.35, 17.99, 14.11, -3.83, -4.20, -4.34, -4.70;
IR ($CHCl_3$) 1737 cm^{-1}; HRMS m/e calcd. for $C_{40}H_{61}O_7Si_3$
737.3725, found 737.33730.

Cyclohexene Ester 10

        A mixture of 380 mg (0.48 mmol) of malonate
9, 23 μL (0.60 mmol) formic acid, 87 μL (0.62
mmol) triethylamine, 10 mg (0.04 mmol)

triphenylphosphine, and 2 mg (0.01 mmol) palladium
acetate in 1.5 mL dioxane was sealed in a 5 mL
hydrolysis tube and heated at 100°C for 12 h.
After evaporation of dioxane, 1 N HCl (1mL) was

5   added, and the mixture was extracted with CH_2Cl_2 (2
mL x 2). The organic solution was washed with
saturated $NaHCO_3$ and dried over $MgSo_4$, filtered,
and concentrated. The oily residue was purified
by column chromatography (0-10% EtOAc/Hexane) to

10   give 310 mg (0.44 mmol, 92%) of cyclohexene ester
10 as a clear oil: R_f=0.50 (25% EtOAc/Hexane); [1]H
NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H),
6.87 (t, J=1.5 Hz, 1H), 5.76 (s, 1H), 4.72 (s,
1H), 4.16 (m, 1H), 3.99 (m, 1H), 3.74 (s, 3H),

15   3.69 (t, J=6.1 Hz, 2H), 2.60 (dt, J=14.3, 5.6 Hz,
1H), 2.10 (ddd, J=16.9, 8.4, 1.5 Hz, 1H), 1.58 (m,
2H), 1.55 (s, 1H), 1.38 (m, 2H), 1.26 (m, 2H),
1.05 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.05 (s,
3H), 0.04 (s, 3H), -0.07 (s, 3H), -0.09 (s, 3H);

20   ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.01, 135.51 (4),
134.05 (2), 133.16, 132.35, 129.45 (2), 127.55
(4), 66.89, 64.16, 51.50, 47.43, 33.1, 26.87,
25.95, 25.92, 25.89, 25.84, 25.68, 23.31, 19.17,
18.42, 18.06, -4.09, -4.37, -4.74, -5.39; IR

25   ($CHCl_3$) 1713 cm^{-1}; HRMS m/e calcd. for $C_{36}H_{57}O_5Si_3$
653.3514, found 653.3516.

Allylic Alcoh l 11

To a 25 mL round-bottomed flask containing 695 mg (0.98 mmol) of cyclohexene ester 10 in 8 mL toluene at -78°C was added 2.15 ml (2.15 mmol) of

5   1 M diisobutylaluminum hydride in toluene dropwise via syringe. The reaction was complete by TLC after 1h. The reaction was quenched by addition at -78°C of 5 mL of 2 M potassium sodium tartrate followed by dilution with 10 mL EtOAc. After the

10   mixture was allowed to warm to room temperature and stirred for 0.5 h, two layers were visible. These were separated and the aqueous layer was washed with EtOAc. The combined organic fractions were washed with water, and brine, and dried over

15   MgSO$_4$, filtered, and concentrated. The residue was purified by column chromatography (0-25% EtOAc/Hexane) to give 518 mg (0.76 mmol, 77%) of allylic alcohol 11 as a clear oil: R$_f$=0.35 (25% EtOAc/Hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 (m,

20   4H), 7.41 (m, 6H), 5.51 (t, J=1.5 Hz, 1H), 4.80 (s, 1H), 4.22 (d, J=12.0 Hz, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 3.74 (s, 3H), 3.69 (t, J=6.1 Hz, 2H), 2.60 (dt, J=14.3, 5.6 Hz, 1H), 2.10 (ddd, J=16.9, 8.4, 1.5 Hz, 1H), 1.58 (m, 2H), 1.55 (s,

25   1H), 1.38 (m, 2H), 1.26 (m, 2H), 1.05 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), -0.07 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.81, 135.51 (4), 134.04 (2),

129.47 (2), 127.55 (4), 122.65, 70.03, 68.32,

65.68, 63.77, 46.36, 33.11, 31.28, 26.85 (3),

25.90 (3), 25.82 (3), 25.51, 25.43, 24.52, 24.03,

19.21, 18.06, -4.20, -4.82 (2), -4.92; IR (CHCl$_3$)

3401, 1713 cm^{-1}; HRMS m/e calcd. for C$_{34}$H$_{57}$O$_4$Si$_3$

625.3565, found 625.3570.

Z-Dienoate 12

To 510 mg (0.75 mmol) of allylic alcohol **11**

in a sealable hydrolysis tube was added 642 mg

(2.2 mmol) triethylphenyl sulfinyl orthoacetate

and 1.0 mg 2,4,6-trimethylbenzoic acid and 2 mL

CH$_2$Cl$_2$. The tube was purged with argon and sealed,

then heated at 100°C for 12h. The reaction

mixture was concentrated. Crude ^{1}H NMR showed a

>10:1 mixture of Z:E isomers. The crude product

was purified via PTLC (10%EtOAc/Hexane) to give

450 mg (0.60 mmol, 80%) of Z dienoate **12** as a

clear oil; R$_f$=0.61 (25% EtOAc/Hexane); ^{1}H NMR (400

MHz, CDCl$_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.61 (s,

1H), 5.17 (t, J=1.8 Hz, 1H), 5.09 (t, J=1.3 Hz,

1H) 4.55 (dd, J=5.5, 1.3 Hz, 2H), 4.12 (q, J=7.2

Hz, 2H), 3.97 (t, J=3.8 Hz, 1H), 3.66 (t, J=6.1

Hz, 2H), 2.48 (dd, J=5.5, 1.4 Hz, 1H), 2.15 (dd,

J=3.8, 1.7 Hz, 1H), 1.70 (m, 1H), 1.58 (m, 2H),

1.55 (s, 1H), 1.38 (m, 2H), 1.26 (m, 2H), 1.04 (s,

9H), 0.87 (s, 18H), 0.05 (s, 6H), 0.04 (s, 6H); ^{13}C

NMR (75 MHz, CDCl$_3$) δ 165.92, 157.09, 153.29,

145.39, 135.52 (4), 134.09 (2), 129.47 (2), 127.55 (4), 117.17, 70.23, 63.91, 59.67, 50.54, 32.98, 26.86 (3), 25.80 (3), 25.74 (3), 19.20, 18.18, 17.98, 14.30, 14.13, -4.66, -4.83, -4.87, -5.17; IR (CHCl$_3$) 3025, 2931, 1713 cm^{-1}; HRMS m/e calcd. for C$_{43}$H$_{70}$O$_5$Si$_3$ 750.4531, found 750.4538.

Phosphine Oxide 13

To a 25 mL round-bottomed flask containing 180 mg (0.24 mmol) of dienoate **12** in 2 mL toluene at -78°C was added dropwise 530 μL (0.53 mmol) of a 1 M solution of diisobutylaluminum hydride via syringe. After 1h the reaction was complete by TLC. The reaction was quenched at -78°C by addition of 2 mL of 2 N potassium sodium tartrate and dilution with 5 mL EtOAc. The mixture was allowed to warm to room temperature and stirred 0.5 h until two distinct phases appeared. The organic phase was separated, and the aqueous phase was washed with EtOAc. The combined organic extracts were washed with water and brine, dried over MgSO$_4$, filtered, and concentrated. The crude mixture was quickly purified by column chromatography (10-20% EtOAc/Hexane) to give 167 mg (0.24 mmol) of the desired allylic alcohol.

To a 10 mL round-bottomed flask containing 152 mg (1.14 mmol) N-chlorosuccinimide in 3 mL CH$_2$Cl$_2$ at 0°C was added 90 mL (1.22 mmol) of

dimethyl sulfide via syringe. A white precipitate
formed immediately upon addition. This mixture was
cooled to -20°C and stirred for 20 minutes. The
above allylic alcohol in 2 mL CH_2Cl_2 was then added
5   to the heterogeneous mixture via cannula. The
reaction was stirred for 0.5 h at -20°C and then
allowed to warm to room temperature and stirred
for an additional 1 h. The organic layer was
washed with water, brine, dried with $MgSO_4$,
10   filtered, and concentrated. The crude product was
passed through florisil (5% EtOAc/Hexane) to
afford 154 mg (0.21 mmol) of the desired allylic
chloride as a yellow oil.

To a 10 mL round-bottomed flask containing
15   the above allylic chloride in 2 mL THF at -78°C
was added dropwise via cannula a 0.5 M solution of
potassium diphenylphosphide in THF. The addition
was stopped once the red color persisted. After 1
h the reaction was allowed to slowly warm to 0°C
20   at which point it was complete by TLC. The
reaction was quenched with 2 drops of water and
the THF was removed. The residue was diluted with
2 mL CH_2Cl_2 and 10 drops of 30% H_2O_2 was added.
After 1 h the reaction was diluted with CH_2Cl_2 and
25   water and the layers were separated. The organic
phase was concentrated. The crude product was
purified by column chromatography (25-50%)
EtOAc/Hexane) to give 121 mg (0.13 mmol, 54% from

Z-dienoate **12**) of the phosphine oxide **13** as a

clear oil: R_f=0.56 (75% EtOAc/Hexane); ^{1}H NMR (400

MHz, CDCl$_3$) δ 7.74-7.36 (m, 20H), 5.3 (dd, J=15.1

Hz, 6.6H), 5.11 (s, 1H), 4.75 (s, 1H), 4.42 (d,

5   J=3.2 Hz, 1H), 3.87 (dd, J=8.9, 4.9 Hz, 1H), 3.65

(t, J=6.6 Hz, 3H), 3.40 (dt, J=15.1, 8.9 Hz, 1H),

3.14 (dt, J=16.0, 6.7 Hz, 1H), 2.4 (dd, J=13.3,

3.2 Hz, 1H), 2.06 (dd, J=14.2, 2.9 Hz, 1H), 1.56

(m, 1H), 1.53 (m, 2H), 1.43 (m, 2H), 1.35 (m, 2H),

10   1.04 (s, 9H), 0.88 (s, 9H), 0.82 (s, 9H), 0.02 (s,

3H), 0.01 (s, 3H), -0.01 (s, 3H), -0.03 (s, 3H);

^{13}C NMR (75 MHz, CDCl$_3$) δ 146.20 (2), 141.17,

135.50 (4), 134.06 (2), 131.71, 131.04, 130.92

(4), 129.45 (2), 128.63 (4), 128.47 (2), 127.53

15   (4), 114.39, 70.15, 63.90, 50.72, 32.97, 30.09,

26.83 (3), 25.79 (3), 25.05, 24.06, 19.18, 18.04,

-4.58, -4.69, -4.89, -5.07; IR (CHCl$_3$) 3025, 2954,

1472, 1255 cm^{-1}; HRMS m/e calcd. for $C_{49}H_{68}O_4Si_3$

835.4163, found 835.4169.

20   **Calcitriol Analogues 3 and 3'**
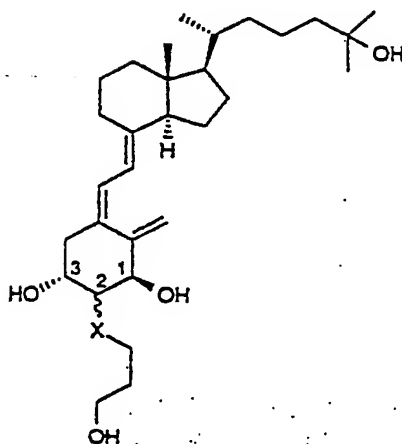
To a 10 mL round-bottomed flask containing 95

mg (0.103 mmol) of phosphine oxide **13** in 1.4 mL of

THF at -78°C was added dropwise 67 μL (0.103 mmol)

of a 1.54 M solution of phenyllithium in THF. The

25   resultant red solution was allowed to stir for 10

minutes. A solution of 20 mg (0.056 mmol) of C-D

ring **14** in 1 mL of THF was added via cannula. The

- 33 -

reaction was complete after 1 h by TLC following disappearance of C-D ring. The reaction was quenched by addition of 1 mL 1:1 $KHCO_3$/2 N potassium sodium tartrate. The layers were

5   separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was rapidly purified by filtration through silica gel using 50% EtOAc/Hexane as solvent to give 47 mg (0.052 mmol,

10   50% yield) of the coupled product. The silyl ethers were cleaved by redissolving the product in 1 mL of THF and treating with 220 μL (0.22 mmol) of tetrabutylammonium fluoride. After 24 h the reaction was diluted with water and the layers

15   were separated, dried over $MgSO_4$, filtered and concentrated. The diastereomers were separated and purified by reverse phase HPLC (30-20% H_2O/CH_3CN on a C-18 semi-prep. column) to afford 1.1 mg (0.002 mmol, 4% yield) of analogue 3, and

20   4.4 mg (0.008 mmol, 16% yield) of analogue 3', both as white solids. ^{1}H NMR of 3 (300 MHz, $CDCl_3$) δ 6.41 (d, J=11.6 Hz, 1H), 6.02 (d, J=11.6 Hz, 1H), 5.29 (s, 1H), 5.02 (s, 1H), 4.35 (s, 1H), 3.82 (m, 1H), 3.68 (t, J=6.1 Hz, 2H), 2.78 (d,

25   J=11.5 Hz, 1H), 2.62 (dd, J=11.5, 3.5 Hz, 1H), 2.20 (dd, J=10.2, 3.5 Hz, 1H), 1.98 (m, 2H), 1.68-1.20 (m), 0.92 (s, 3H), 0.90 (s, 3H), 0.54 (s, 3H). ^{1}H NMR of 3' (300 MHz, $CDCl_3$) δ 6.40 (d,

J=11.6 Hz, 1H), 5.98 (d, J=11.6 Hz, 1H), 5.27 (s,

1H), 4.98 (s, 1H), 4.38 (s, 1H), 3.87 (m, 1H),

3.68 (t, J=6.1 Hz, 2H), 2.82 (d, J=11.5 Hz, 1H),

2.65 (dd, J=11.5, 3.5 Hz, 1H), 2.24 (dd, J=10.2,

5   3.5 Hz, 1H), 1.68-1.20 (m), 0.92 (s, 3H), 0.90 (s,

3H), 0.52 (s, 3H); UV-Vis (MeOH) λ_{max} 268 nm (ϵ

15,600); HRMS m/e calcd. for $C_{31}H_{50}O_3$ 470.3760,

found 470.3771.

2-Fluorides

10   The above-described methods for producing the

vitamin D_3 analogues with alcohols substituted in

the 2-position can be readily modified to produce

comparable analogues with fluorides substituted in

the two position (18-21). Table IV lists the

15   fluoride analogues of the present invention.

- 35 -

TABLE IV

2-SUBSTITUTED FLUORIDES OF CALCITRIOL

Position

3	2	1
3β	$2\alpha-(CH_2)_4F$	1α
3α	$2\beta-(CH_2)_4F$	1β
3β	$2\alpha-(CH_2)_3F$	1α
3α	$2\beta-(CH_2)_3F$	1β

The following scientific articles and references have been cited throughout this application and the entire contents of each article or reference is hereby incorporated by

5   reference.

Scientific Articles

1.   Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y; Itai, A.; Shudo, K.; *J. Am. Chem. Soc.*, **1991**, *113*, 5474 and references

10   therein.

2.   Tilyard, M.W. in "Vitamin D: Gene Regulation, Structure-Function Analysis, and Clinical Applications", A.W. Norman, R. Bouillon, M. Thomasset, Eds., W. de Gruyter, NY, **1991**, p.

15   779.

3.   Nordin, B.E.C.; Need, A.G.; Morris, H.A.; Horowitz, M. in "Vitamin D: Gene Regulation, Structure-Function Analysis, and Clinical Applications", A.W. Norman, R. Bouillon, M.

20   Thomasset, Eds., W. de Gruyter, NY, **1991**, p. 787.

4.   a) Nishii, Y.; Abe, S.; Kobayashi, T.; Okano, T.; Tsugawa, N.; Slatopolsky, E.; Brown, A.J.; Dusso, A.; Raisz, L.G. in "Vitamin D: Gene Regulation, Structure-Function Analysis, and Clinical Applications", A.W. Norman, R. Bouillon,

25   R. Thomasset, Eds., W. de Gruyter, NY, **1991**, p. 294; b) Okano, T.; Tsugawa, N.; Masuda, S.; Takeuchi, A.; Kobayashi, T.; Takita, Y.; Nishii, Y.; *Biochem. Biophys. Res. Commun.*, **1989**, *163*,

30   1444; c) Miyamoto, K.; Murayama, E.; Ochi, K.; Watanabe, H.; Kubodera, N.; *Chem. Pharm. Bull.*, **1993**, *41*, 1111.

5.   a) Posner, G.H.; Nelson, T.D.; Kinter, C.M.; Johnson, N.; *J. Org. Chem.*, **1992**, *57*, 4083;

35   b) Posner, G.H.; Nelson, T.D.; Kinter, C.M., Afarinkia, K.; *Tetrahedron Lett.*, **1991**, *32*, 5295; c) Afarinkia, K.; Posner, G.H.; *Ibid*, **1992**, *33*, 7839; d) for a review, see Afarinkia, K.; Vinader, V.; Nelson, T.D.; Posner, G.H.; *Tetrahedron*, **1992**,

40   *48*, 9111.

6. a) Gupta, R.B.; Frank, R.W.; *J. Am. Chem. Soc.*, **1987**, *109*, 5393; b) Jensen, F.; Foote, C.S.; *Ibid*, **1987**, *109*, 6376; c) Baran, J.; Mayr, H.; Ruster, V.; Klarner, F.G.; *J. Org. Chem.*, **1989**, *54*, 5016; d) Gassman, P.G.; Gorman, D.B.; *J. Am. Chem. Soc.*, **1990**, *112*, 8624; e) Reissig, H-U.; Hippeli, C.; Arnold, T.; *Chem. Ber.*, **1990**, *123*, 2403; f) Van Mele, B.; Huybrechts, G; *Int. J. Chem. Kinetics*, **1989**, *21*, 967; g) Sauer, J.; Lang, D.; Wiest, H.; *Chem. Ber.*, **1964**, *97*, 3208; g) *cf.* Li, Y.; Houk, K.N.; *J. Am. Chem. Soc.*, **1993**, *115*, 7478 and references therein.

7. a) Karplus, M.; *J. Chem. Phys.*, **1959**, *30*, 11; b) Karplus, J.; *J. Am. Chem. Soc.*, **1963**, *85*, 2870; c) Jackman, L.M.; Sternhell, S.; *Applications of NMR Spectroscopy in Organic Chemistry*, 2nd Ed.; Pergamon, NY, **1969**.

8. a) Posner, G.H., Kinter, C.M.; *J. Org. Chem.*, **1990**, *55*, 3967; b) Posner, G.H.; Nelson, T.D.; *Tetrahedron*, **1990**, *46*, 4573; c) Posner, G.H.; Wettlaufer, D.G.; *J. Am. Chem. Soc.*, **1986**, *108*, 7373.

9. Moeller, K.D.; Tinao, L.V.; *J. Am. Chem. Soc.*, **1992**, *114*, 1033 and references therein.

10. 2-Pyrone, prone to rapid polymerization under thermal conditions, undergoes non-regioselective cycloadditions under very high pressure conditions (e.g. 18.5 Kbar): Markó, I.E.; Seres, P.; Swarbrick, T.M.; Staton, I.; Adams, H.; *Tetrahedron Lett.*, **1992**, *33*, 5649.

11. Posner, G.H.; Carry, J.-C.; Anjeh, T.E.N.; French, A.N.; *J. Org. Chem.*, **1992**, *57*, 7012.

12. Mandi, T.; Imaji, M.; Takada, H.; Kawata, M.; Nokami, J.; Tsuji, J.; *J. Org. Chem.*, **1989**, *54*, 5395.

13. a) Posner, G.H.; Crouch, R.D.; Kinter, C.M.; Carry, J.-C.; *J. Org. Chem.*, **1991**, *56*, 6981; b) Posner, G.H.; Dai, H.; *BioMed. Chem. Lett.*, **1993**, *3*, 1829.

14. Lythgoe, B.; Moran, T.A.; Nambudiry, M.E.N.; Tideswell, J.; Wright, P.W.; *J. Chem. Soc. Perkin Trans. 1*, **1978**, 590.

15.   Posner, G.H.; Nelson, T.C.; Guyton,
K.Z.; Kensler, T.W.; *J. Med. Chem.*, **1992**, *35*,
3280.

16.   Unpublished results of G.H. Posner and
H. Liu.

17.   Unpublished results of G.H. Posner, T.
D. Nelson, and C.H. Oh.

18.   Filler, R. et al. (Eds.); *Organofluorine
Compounds in Medicinal Chemistry and Biomedical
Applications*, Elsevier Science Publishers, **1993**.

19.   Kobayashi, Y; Nakazawa, M.; Kumadaki,
I., Taguchi, T., Ohshima, E.; Ikekawa, N.; Tanaka,
Y.; DeLuca, H.F.; *Chem. Pharm. Bull.*, **1986**, *34*,
1568-1572.

20.   Ohshima, E.; Sai, H.; Takatsuto, S.;
Ikekawa, N.; Kobayashi, Y.; Tanaka, Y.; DeLuca,
H.F.; *Chem. Pharm. Bull.*, **1984**, *32*, 3525-3531.

21.   Oshida, L-i; Morisaki, M.; Ikekawa, N.;
*Tetrahedron Lett.*, **1980**, *21*, 1755-1756.

While the invention has been described in
connection with what is presently considered to be
the most practical and preferred embodiments, it
is to be understood that the invention is not to
be limited to the disclosed embodiments, but on
the contrary is intended to cover various
modifications and equivalent arrangements included
within the spirit and scope of the appended
claims.
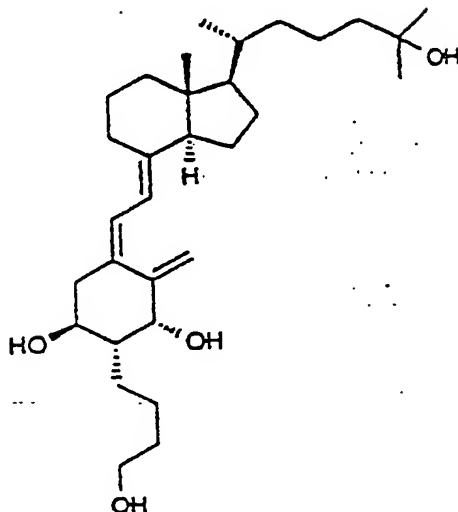
WHAT IS CLAIMED IS:

1. A vitamin D_3 analogue which includes a substituent in the 2-position selected from the group consisting of alcohols and fluorides.

5   2. The analogue of claim 1 wherein said substituent is $-(CH_2)_4OH$.

3. The analogue of claim 2 having the following structural formula:
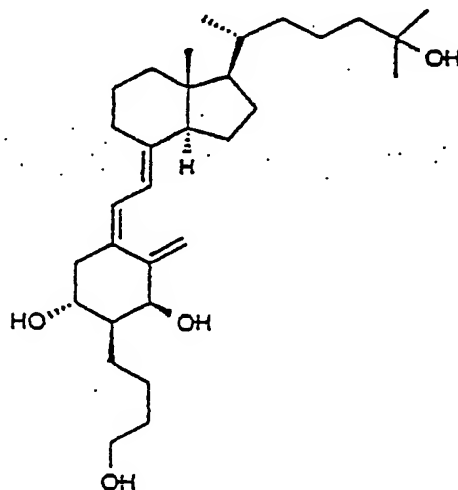
4. The analogue of claim 2 having the following structural formula:

5. The analogue of claim 1 wherein said substituent is $-(CH_2)_3F$.

6. The analogue of claim 1 wherein said substituent is $-(CH_2)_4F$.

7. A method for the preparation of a vitamin D_3 analogue which includes an alcohol substituent in the 2-position, comprising the steps of:

a) subjecting methyl 2-pyrone-3-carboxylate and a silylated vinylic ether to high pressure cycloaddition to form a bicycloadduct;

b) reacting the bicycloadduct with lithium allyloxide to produce a mixed methyl allyl malonate;

c) decarboxylating the mixed methyl allyl
malonate with palladium acetate to yield a
cyclohexene ester;

d) silylating and reducing the cyclohexene
5 ester to form an alcohol;

e) subjecting the allylic alcohol to a
Claisen rearrangement followed by spontaneous
thermal sulfoxide elimination to form a
Z-dienoate;

10 f) reacting the Z-dienoate with a hydride to
form an allylic alcohol;

g) reacting the allylic alcohol with N-
chlorosuccinimide and dimethyl sulfide to form an
allylic chloride;

15 h) reacting the allylic chloride with
diphenylphosphide and then with hydrogen peroxide
to form a phosphine oxide;

i) reacting the phosphine oxide with
phenyllithium to produce a conjugate base of the
20 phosphine oxide;

j) coupling the conjugate base of phosphine
oxide with a C,D-ring ketone to produce O-
silylated derivatives of diastereomeric 2-(4'-
hydroxylated) calcitriol analogues; and

25 k) separating and isolating the analogues.

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 401/00

US CL :552/653

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 552/653; C07C 401/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	US, A, 5,389,622 (POSNER ET AL.) 14 February 1995, see entire document.	1-4
X	JP, A, 6-41059 (NAKASOTO SEIYAKU KK) 15 February 1994, see entire document.	1, 2, 4
-- Y		1-6
P, X	JOURNAL OF ORGANIC CHEMISTRY, VOLUME 59, NUMBER 25, ISSUED 16 DECEMBER 1994, POSNER ET AL., "STEREOCONTROLLED TOTAL SYNTHESIS OF CALCITRIOL DERIVATIVES: 1,25-DIHYDROXY-2-(4'-HYDROXYBUTYL) VITAMIN D ANALOGS OF AN OSTEOPOROSIS DRUG, PAGES 7855-7861.	1-4

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

*	Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	
"E"	earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	
"P"	document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 JUNE 1995	29 SEP 1995

Name and mailing address of the ISA/US	Authorized Officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	KIMBERLY J. KESTLER jd
	Telephone No. (703) 308-1235